REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 9-35 remain pending in the application subsequent to entry of this Amendment.

The Official Action raises lack of clarity issues directed to specific claims. In item 1 the claims in general are objected to as to the misspelling of liposomes. In fact, the word is misspelled twice in claim 19 only and these misspellings are corrected in the above instructions.

The various embodiments of the invention given in claim 34 are the subject of criticism of allegedly being indefinite, so the claims have been amended to clarify what is meant by "a salt having surface activity" in claim 19 and various embodiments of claim 34 are removed in order to advance examination and reduce issues.

As to the rejection to the "eye cream" in claim 34 applicants disagree because the term "eye cream" is generally in the cosmetic and beauty arts intended to be a product that is applied to the whole contour area of the eyes, not limited to only eyelids. The term "eye cream" is generally recognized in this art and claim 34 is clear and readily understood as it is amended above.

The claims are also amended in order to more particularly point out and distinctly claim that which applicants regard as their invention and to include the preferred aspects of the description.

The method of the invention is conducted without the use of a surfactant other than the phospholipid and this is discussed generally at pages 2-3 where various prior procedures require a separate ionic surfactant or the like in order to prepare a mixed micelle system. The process is also conducted without intense mechanical treatment as discussed specifically at page 5, line 6 and the associated discussions on page 3. Both of these features form part of the prior art but are not included in the present invention, hence basis for the changes made to claim 19 will be apparent from the description of the invention in its entire context.

Responsive to the examiner's comments in item 3, second paragraph of the current Action, specifically the contention that the pH range 5-8 in step (b) of claim 19 is unclear, the inventor commented that the pH range of the emulsion is determined depending on the chemical features of the triterpenoid used, i.e. on the pKa of the triterpenoid. Specifically, pKa is defined as the constant when the proton donor tendency of the substance is equilibrium to the proton

accepter tendency of the surrounding medium. When the acid triterpenoid is protonated, it forms a triterpenoid salt having surface activity, and when the triterpenoid salt is deprotonated, it loses a surface activity.

Thus the surface activity of the triterpenoid is determined on the basis of the pKa range of the triterpenoid, and the pKa range of the triterpenoid used in this invention is about 5-8, and thus the pH range of the medium is also determined as 5-8. For example, when the pKa constant of the triterpenoid used is 6, the triterpenoid is converted to a surface-active salt when the pH of the surrounding medium is well above 6, and when the pH of the medium is lowered to about 6, the salt converts back to the acid form and loses its surface activity. Likewise, when the pKa constant of the triterpenoid used is 8, the triterpenoid is converted to a surface-active salt when the pH of the surrounding medium is well above 8, and when the pH of the medium is lowered to about 8, the salt converts back to acid form and loses its surface activity. Applicants submit claim 19 as it now stands is clear and accurate. Should the examiner prefer a different form of expression, please contact the undersigned.

It is submitted that the amendments made to claims 19 and 34 resolve the issues stated in items 1-4 of the Official Action, thus withdrawal of the objections and rejections in these four items is requested.

Claims 29 and 31-35 are rejected as being anticipated by WO 01/17532 but, unfortunately, is based upon a misunderstanding of the claims at issue. The claims are directed to preparing terpenoid-containing liposomes and are directed to methods. In contrast, the claims appear to be examined as "product-by-process" as stated on page 4, first full paragraph, last sentence of the current Official Action. That is not an accurate representation of the claims now in issue.

The balance of the Official Action includes four separate rejections of various groups of claims as allegedly being "obvious" over three documents Touitou, Cauwenberg and the newly cited U.S. patent to Hauser and these documents are applied either by themselves or in combination. In this response, focus will be directed to these three specific references as they are featured in the first rejection (page 4, item 2) and then repeated and expanded in the three separate rejections that follow.

Claim 19 is cast in Jepson format to emphasize the technical features of step (a) -- base addition – and step (b) – acid addition. In step (a), adding a base to the dispersion of step (1) transforms the triterpenoid into its salt which has surface activity; note page 6, lines 7-8. Then, in step (b), when the acid is added to decrease the pH in a range of 5-8 -- this transforms the triterpenoid back to its original form which causes its surface activity to disappear resulting in changing the mixed micelle system to submicron-sized liposomes; *see* in particular page 6, lines 11-14.

Applicants prepare triterpenoid-containing liposomes by (a) dispersing a triterpenoid having an acid moiety in a polyol while heating; (b) adding a base into the dispersion of step (a) thereby converting the acid group in the triterpenoid to a salt to prepare a low viscosity dispersion. Separately (c) phospholipid is dissolved in ethanol at room temperature to prepare an ethanol solution of phospholipids, then (d) adding the ethanol solution of step (c) into the dispersion of step (b) to prepare a mixture. This mixture is then (e) added to distilled water and then emulsified to prepare an emulsion; and finally (f) adding an acid to the emulsion of step (e) to convert the triterpenoid salt of step (b) back to the acid form. This results in liposomes having diameters in a range of 0.001~10μm and containing the triterpenoid in a range of 0.001~5% by weight based on the total weight of the liposome.

Considering then procedures claimed by applicant used to prepare their triterpenoid-containing liposomes, pH regulation is a key factor.

Regarding pH regulation

Regulating pH by using a base and then using acid in the present invention is to prepare liposome containing a triterpenoid at a high concentration. This is totally different from regulating the pH of the cosmetic composition containing liposome merely in order to be compatible with skin.

More specifically, the object of the present invention is to provide liposomes containing a triterpenoid at high concentration while using a non-toxic solvent without intensive mechanical treatment. In order to incorporate triterpenoid at a high concentration uniformly into a liposome, the present invention employs triterpenoid having acid group, and by adding a base, the triterpenoid is transformed into its salt having surface activity. The transformed triterpenoid salt acts as a surfactant of high HLB, and it forms a mixed micelle system when mixed with a low

HLB lipid. Then, the above-obtained mixed micelle system maintains its pH in a range of 10~11. By adding an acid to decrease its pH to 5~8, the triterpenoid salt transforms back to the original form having an acid group, and thereby loses its surface activity. This results in changing the mixed micelle system into a liposome. During the transformation, triterpenoid is loaded into the liposome at high concentration. *(see* column 2, third paragraph of specification of the present invention.) In other words, regulating pH by using a base and then using acid in the present invention is to prepare liposome containing triterpenoid at high concentration.

However, Cauwenbergh discloses that the final pH of 5~7.5 of a skin formulation is preferable and this pH can be obtained by the addition of either a base or an acid or buffer. Cauwenbergh discloses pH regulation of a skin formulation containing liposomes merely in order to be compatible with skin, not pH regulation in the preparation of liposome as in the present invention.

Regarding use of Triethanolamine (TEA)

Touitou merely discloses the use of TEA in the example of a gel preparation, but it does not disclose the reason why TEA is added to the gel preparation. In addition, Touitou does not disclose or suggest the combined use of base and triterpenoid of the present invention, i.e., to transform triterpenoid having acid moiety into its salt having surface activity so as to form mixed micelle system with low HLB lipid.

Further, Touitou does not disclose or suggest the use of acid to transform the triterpenoid salt back into its original form having an acid group, resulting in changing the mixed micelle system into a liposome, whereby triterpenoid is loaded into the liposome at high concentration.

In addition, the use of TEA in Delrieu (page 7, middle paragraph of the Action) is to prevent aggregation of liposomes, i.e., to stabilize the liposomes already prepared, which is different from that of the present invention which is to prepare liposome triterpenoid at high concentration.

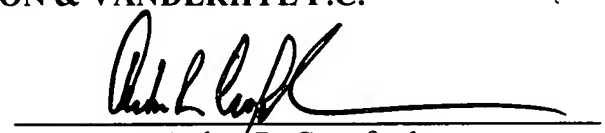
The deficiencies in the first "obviousness" rejection advanced in the Official Action continue through the three additional obviousness rejections and it is not believed to be necessary to discuss these in great detail as substantially the same issues namely pH regulation and the use of TEA are included in these three separate rejections.

It is noted that six references in item 4 and 7 references in item 5 have been asserted as the basis of the Examiner's third and fourth obviousness rejections. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961); *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 U.S.P.Q. 121, 124 (7th Cir. 1950); *Reynolds et al v. Whitin Machine Works*, 167 F.2d 78, 83, 76 U.S.P.Q. 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 U.S.P.Q. 902, 927 (N.D. Ala. 1980).

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited. Should the examiner require further information, please contact the undersigned.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

Arthur R. Crawford
Reg. No. 25,327

ARC:eaw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100